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ORIGINAL ARTICLE

Limited benefit of targeted molecular therapy for inferior vena cava thrombus associated with renal cell carcinoma

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Abstract
Background The clinical benefit of targeted molecular therapy (TMT) for an inferior vena cava (IVC) tumor thrombus associated with renal cell carcinoma (RCC) is unclear. The aim of the present study was to assess the change in IVC thrombus height during TMT and to identify the factors associated with the effect of TMT on an IVC thrombus in RCC patients.
Methods The present study retrospectively analyzed 21 patients with an IVC thrombus who were treated with TMT at our hospital. Thrombus height and level before and after TMT were assessed using CT or MRI. Furthermore, we examined the factors associated with the effect of TMT on the IVC thrombus.
Results The tumor thrombus level before TMT was I in 2 patients (10%), II in 10 (47%), III in 4 (19%), and IV in 5 (24%). Following TMT, the tumor thrombus height decreased in 16 patients (76%), and the mean decrease was 17 mm. The tumor thrombus height increased in 5 patients (24%), and the mean increase was 30 mm. The tumor thrombus level decreased in 4 patients (19%), remained stable in 15 patients (71%), and increased in 2 patients (10%). We found that the clinical nodal stage ($p = 0.025$) was significantly associated with and the serum neutrophil count ($p = 0.067$) tended to be associated with the reduction in the IVC thrombus.
Conclusion The clinical benefit of TMT for an IVC thrombus associated with RCC is limited.

Keywords Renal cell carcinoma · Tumor thrombus · Targeted molecular therapy

Introduction

Renal cell carcinoma (RCC) invading into the renal vein and/or inferior vena cava (IVC) is noted in about 4–10% of all patients with RCC [1, 2]. The standard treatment for patients with RCC extending into the IVC is radical nephrectomy and tumor thrombectomy [3]. The surgical management of RCC invading into an IVC thrombus has been shown to be associated with high morbidity and mortality rates [4] and an overall complication rate of 38% [5]. The perioperative mortality rate has been reported to be 5–10% [6, 7]. Karnes et al. reported that both major and minor complications were highly associated with the level of IVC tumor thrombus [8]. Pre-surgical systemic therapies are expected to improve the safety and feasibility of the surgical procedure by decreasing the thrombus burden and level.

Initially, cytokine therapy was used as systemic therapy for metastatic RCC; however, recently, targeted molecular therapy (TMT) has been reported to reduce the tumor burden more effectively and prolong survival in patients with metastatic RCC [9–11]. In the current literature, the effect of TMT on an IVC thrombus has been reported [12, 13]. However, the clinical benefit of TMT for an IVC tumor thrombus associated with RCC is unclear. Some previous case reports noted that TMT was effective against an IVC thrombus [12, 14–19], while two retrospective studies

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demonstrated sufficient effects of TMT [13, 20] in selected RCC patients. Furthermore, the factors associated with the effect of TMT on an IVC thrombus in patients with RCC and the efficacy relationship between the IVC thrombus and the primary tumor are not known.

Therefore, the study presented here aimed to assess the clinical benefit of TMT for an IVC thrombus associated with RCC and to identify the factors associated with the effect of TMT on an IVC thrombus in patients with RCC.

Patients and methods

Patients

In the present study, we retrospectively reviewed the medical records of patients at Tokyo Women's Medical University Hospital to identify RCC patients with an IVC tumor thrombus treated with TMT between June 2008 and September 2015. Twenty-one patients with RCC were eventually considered for inclusion. The study was approved by the institutional review board of Tokyo Women's Medical University. Informed consent for the treatment and evaluation was obtained from all the patients.

Study design

The main outcome was the radiographically measured change in height of the IVC tumor thrombus and the clinical level following treatment with TMT. Additionally, we examined the primary tumor response to TMT. Furthermore, we investigated the factors associated with the effect of TMT on the IVC thrombus and examined the effect of each TMT on the IVC thrombus.

Targeted molecular therapy

In the present study, we used four targeted agents: sunitinib, sorafenib, pazopanib, and temsirolimus. There were two indications for the administration of TMT. The first indication was in the pre-surgical setting, and TMT was initiated with the aim of reducing the thrombus volume or inhibiting further growth of the tumor thrombus before surgery. In the pre-surgical setting, TMT was continued for 1–2 courses before surgery; however, 1 patient who was administered TMT at another hospital received 6 courses of TMT. The treatment was discontinued 3–7 days before surgery at the physician's discretion. The resumption of TMT was considered at least 14 days after surgery when wound healing was confirmed. The second indication was at systemic therapy for patients with inoperable disease.

Evaluation

We retrospectively collected clinical information, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index, TMT type, laboratory findings, 2010 TNM stage, tumor thrombus height (defined as the distance in mm between the renal vein and upper extension of the thrombus), tumor thrombus levels before and after TMT, and side of the tumor, and pathological information from the percutaneous biopsy sample or surgical specimen. The tumor thrombus was defined according to the classification proposed by the Mayo Clinic [7]. Briefly, a

Table 1 Patient background characteristics

Characteristic	Value ($n = 21$)
Age (years), median (range)	68 (47–82)
Sex, *n* (%)	
Male	16 (76)
Female	5 (24)
ECOG PS, *n* (%)	
0	2 (10)
1	17 (80)
2	2 (10)
Reason for TMT	
Pre-surgical therapy, *n* (%)	11 (52)
Not a candidate for surgery, *n* (%)	10 (48)
TMT, *n* (%)	
Sunitinib	17 (81)
Sorafenib	1 (5)
Pazopanib	2 (9)
Temsirolimus	1 (5)
Duration of therapy (months), median (range)	3 (0.8–21)
Clinical stage of the tumor, *n* (%)	
T3b	14 (67)
T3c	6 (28)
T4	1 (5)
Nodal stage, *n* (%)	
N0	17 (80)
N1	2 (10)
N2	2 (10)
Metastatic disease, *n* (%)	11 (52)
Tumor thrombus level, *n* (%)	
I	2 (10)
II	10 (47)
III	4 (19)
IV	5 (24)
Thrombus height above renal vein before TMT (mm), median (range)	63 (10–170)

TMT targeted molecular therapy, *ECOG PS* Eastern Cooperative Oncology Group performance status

tumor thrombus found in the renal vein extending <2 cm within the IVC was classified as level I; an infrahepatic thrombus extending ≥2 cm within the IVC was classified as level II; an intrahepatic IVC thrombus below the diaphragm was classified as level III, and an IVC tumor thrombus extending above the diaphragm was classified as level IV.

Measurement of the effect

Treatment efficacy was assessed every 1 or 2 months using computed tomography (CT) or magnetic resonance imaging (MRI).

Statistical analysis

The association between two continuous variables was evaluated with the Pearson correlation coefficients. After categorizing the patients into a decreased group (tumor thrombus decreased following TMT) and an increased group (tumor thrombus did not decrease), all clinical, laboratory, radiographic, and pathological data were compared between the two groups using nonparametric methods with a chi-square or Fisher exact test for categorical data and the Mann–Whitney *U* test for continuous data. All statistical analyses were performed using JMP software (ver. pro12; SAS Institute, Cary, NC, USA). A p value <0.05 (two-sided) was considered to indicate significance.

Results

Patient background

A total of 21 patients were treated for RCC with an IVC thrombus using TMT between June 2008 and September 2015 in our hospital (Table 1). Among the 21 patients, 11 (52%) received TMT as pre-surgical therapy and 10 (48%) received it because they were not candidates for surgery. The median patient age was 68 years (range 47–82 years), and 16 patients (76%) were male. The ECOG PS was 0 in 2 patients (10%), 1 in 17 (80%), and 2 in 2 (10%). The median tumor thrombus height from the renal vein before TMT was 63 mm (range 10–170 mm). The tumor thrombus level before TMT was I in 2 patients (10%), II in 10 (47%), III in 4 (19%), and IV in 5 (24%). Of the 21 patients, 17 (81%) received sunitinib, 1 (5%) received sorafenib, 2 (9%) received pazopanib, and 1 (5%) received temsirolimus. TMT was administered for a median of 3 months (range, 0.8–21 months). Additionally, 11 patients (52%) underwent tumor thrombectomy after TMT.

Effect of TMT on the IVC tumor thrombus and primary tumor

We examined the effect of TMT on the IVC tumor thrombus and primary tumor in our patients by using CT or MRI (Fig. 1; Table 2). Following TMT, the median

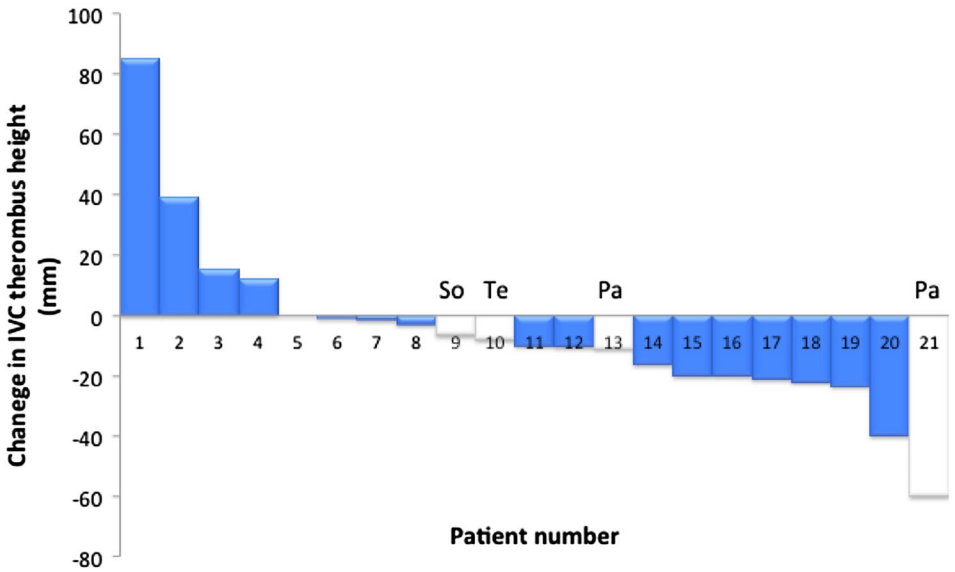

Fig. 1 Effect of targeted molecular therapy on an IVC thrombus associated with renal cell carcinoma. The *blue columns* represent the cases receiving sunitinib, while the *white columns* represent the cases receiving TMTs other than sunitinib. TMTs other than sunitinib are described *above the white columns*. *IVC* inferior vena cava, *So* sorafenib, *Te*, temsirolimus *Pa* pazopanib

Table 2 Effects of TMT on the IVC thrombus and primary tumor

IVC thrombus	
Thrombus height	
Change in thrombus height following TMT (mm), median (range)	−10 (−60 to 85)
Increased thrombus height, *n* (%)	5 (24)
Decreased thrombus height, *n* (%)	16 (76)
Thrombus level	
Increased thrombus level, *n* (%)	2 (10)
No change in the thrombus level, *n* (%)	15 (71)
Decreased thrombus level, *n* (%)	4 (19)
Primary tumor	
Change in the maximum diameter following TMT (mm), median (range)	−6 (−20 to 15)
Increased maximum diameter, *n* (%)	4 (27)
Decreased maximum diameter, *n* (%)	11 (73)

TMT targeted molecular therapy, *IVC* inferior vena cava

change in thrombus height was −10 mm (range −60 to 85 mm). The tumor thrombus height decreased in 16 patients (76%), and the mean decrease was 17 mm. The tumor thrombus height increased in 5 patients (24%), and the mean increase was 30 mm. The tumor thrombus level decreased in 4 patients (19%), remained stable in 15 patients (71%), and increased in 2 patients (10%). One of the two patients with an increased tumor thrombus level showed an increase in IVC tumor thrombus height of as much as 85 mm. Although TMT was administered as pre-surgical therapy in this patient, the patient developed a pulmonary embolism and could not undergo surgical management.

The primary tumor could be evaluated in 15 patients, while it could not be evaluated in 6 patients who had previously undergone nephrectomy. Following TMT, the median change in the maximum diameter of the primary tumor was −6 mm (range −20 to 15 mm). During TMT, the maximum diameter of the primary tumor increased in 4 of the 15 patients (27%) and decreased in 11 of the 15 patients (73%). In addition, the association between the effect of TMT on the IVC tumor thrombus and that on the primary tumor was evaluated (data not shown), and we did not identify a significant association ($r = -0.19$, $p = 0.50$). Representative images of the histological change after TMT are shown in Fig. 2.

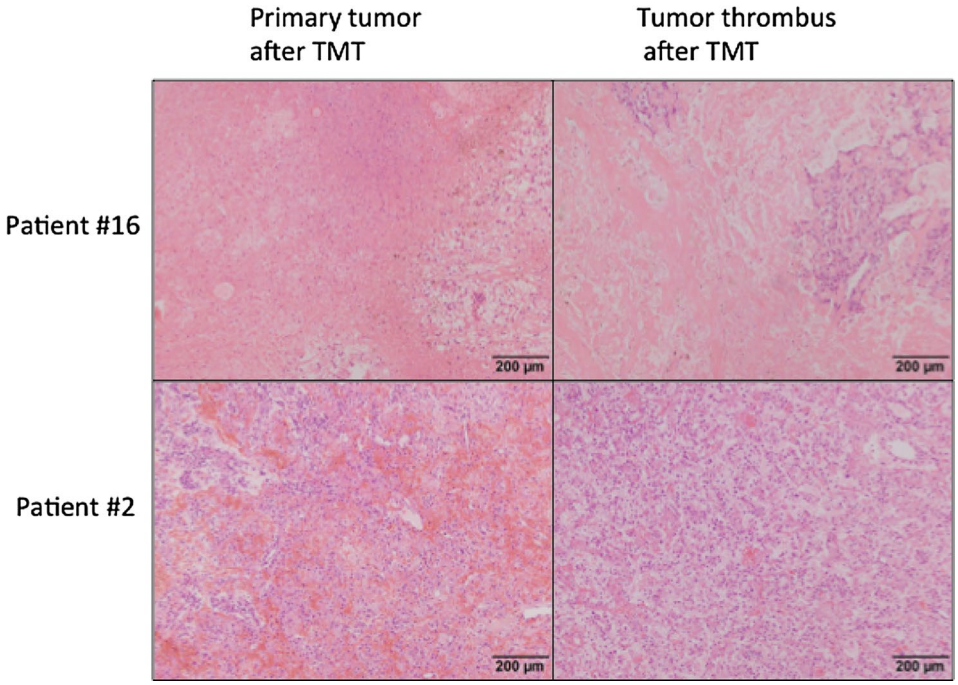

Fig. 2 Microscopic findings of the primary tumor and tumor thrombus treated with TMT in two patients. These cases are representative of those undergoing resection of the primary tumor and tumor thrombus after TMT. The *two photographs on the left* are of the primary tumors and the *two photographs on the right* are of the tumor thrombus (hematoxylin–eosin, original magnification ×100). Patient #16 showed a symmetric response with regard to the primary tumor and tumor thrombus (primary tumor, decrease of 20 mm; tumor thrombus, decrease of 20 mm). Widespread necrotic tissues are seen in both the primary tumor and tumor thrombus after TMT. In contrast, patient #2 showed an asymmetric response with regard to the primary tumor and tumor thrombus (primary tumor, decrease of 12 mm; tumor thrombus, increase of 39 mm). Hemorrhagic necrosis is seen in the primary tumor, while viable tumor cells are seen in the tumor thrombus after TMT

Examination of the clinicopathologic factors associated with the reduction in the IVC thrombus with TMT

To examine the clinicopathologic factors associated with the efficacy of TMT for an IVC thrombus in RCC patients, we clinicopathologically compared the factors between the decreased and increased groups (Table 3). We found significant differences between the two groups with regard to clinical nodal stage ($p = 0.025$), although the presence of lymphadenopathy before TMT was not statistically significant. Additionally, the serum neutrophil count tended to be different ($p = 0.067$). However, no significant differences were noted for any other factors.

IVC tumor thrombus reduction with each TMT

The median change in thrombus height following TMT was −10 mm (range −40 to 85 mm) in 17 patients who received sunitinib, −6.5 mm (range not determined) in 1 patient who received sorafenib, −36 mm (range −60 to −11 mm) in 2 patients who received pazopanib, and -8 mm (range not determined) in 1 patient who received temsirolimus.

Discussion

The present study found that the clinical benefit of TMT for an IVC tumor thrombus associated with RCC was limited. Furthermore, RCC patients with an IVC tumor thrombus having a clinical nodal stage of N2 or higher neutrophil count showed a poor benefit from TMT.

Karakiewicz et al. reported a case in which neoadjuvant sunitinib therapy effectively reduced the IVC tumor thrombus [12]. In our study, the tumor thrombus height decreased after TMT in 76% of the patients and the tumor thrombus level decreased in 19%; however, the tumor thrombus height increased in 24% and the tumor thrombus level increased in 10%. Consistent with the findings of our study, Cost et al. showed that only 12% of patients with an IVC tumor thrombus treated using TMT showed a decrease in the thrombus-level classification, while 4% of patients showed an increase in the thrombus-level classification among 25 patients [13]. Additionally, Bigot et al. performed a retrospective study of 14 patients treated with TMT and reported that 7% of the patients showed an increase in the thrombus level and only 7% showed a decrease in the thrombus level [20]. These results collectively suggest that the efficacy of TMT at reducing the

Table 3 Comparison of patient and tumor characteristics between the decreased and increased groups

	Decreased	Increased	*p* value
	($n = 16$)	($n = 5$)	
Age (years), median (range)	67 (47–82)	68 (57–69)	0.59*
Sex, *n* (%)			
Male	11 (69)	5 (100)	0.075#
Female	5 (31)	0 (0)	
ECOG PS, *n* (%)			
0	2 (13)	0 (0)	0.50#
1	13 (81)	4 (80)	
2	1 (6)	1 (20)	
Reason for TMT, *n* (%)			
Pre-surgical therapy, *n* (%)	8 (50)	3 (60)	0.70#
Not a candidate for surgery, *n* (%)	8 (50)	2 (40)	
Status of nephrectomy before TMT			
N0, *n* (%)	10 (63)	3 (60)	0.92#
N+, *n* (%)	6 (37)	2 (40)	
TMT, *n* (%)			
Sunitinib	12 (75)	5 (100)	0.67#
Sorafenib	1 (6)	0 (0)	
Pazopanib	2 (13)	0 (0)	
Temsirolimus	1 (6)	0 (0)	
Duration of therapy (months), median (range)	3.5 (1.5–21)	2 (0.8–3)	0.12*

Table 3 continued

	Decreased	Increased	*p* value
Relative dose intensity of TMT (%), median (range)	66 (28–85)	50 (50–63)	0.21*
Clinical stage of tumor, *n* (%)			
T3b, *n* (%)	9 (56)	5 (100)	0.19#
T3c, *n* (%)	6 (38)	0 (0)	
T4, *n* (%)	1 (6)	0 (0)	
Clinical nodal stage, *n* (%)			
N0, *n* (%)	14 (88)	3 (60)	0.025#
N1, *n* (%)	2 (12)	0 (0)	
N2, *n* (%)	0 (0)	2 (40)	
Presence of lymphadenopathy before TMT, *n* (%)			
No, *n* (%)	14 (88)	3 (60)	0.19#
Yes, *n* (%)	2 (12)	2 (40)	
Metastatic disease, *n* (%)	8 (57)	3 (60)	0.70#
Tumor thrombus level, *n* (%)			
I, *n* (%)	1 (6)	1 (20)	0.27#
II, *n* (%)	8 (50)	2 (40)	
III, *n* (%)	2 (13)	2 (40)	
IV, *n* (%)	5 (31)	0 (0)	
Thrombus height above the renal vein before TMT (mm), median (range)	70 (10–170)	43(19–119)	0.29*
Histology			
Clear cell RCC, *n* (%)	8 (50)	2 (40)	0.76#
Papillary cell RCC type 2, *n* (%)	2 (12.5)	1 (20)	
Sarcomatoid change, *n* (%)	2 (12.5)	0 (0)	
Unknown, *n* (%)	4 (25)	2 (40)	
Corrected calcium (mg/dL), median (range)	9.3 (8.7–10.4)	9.2 (8.8–9.7)	0.78*
Neutrophil count (/μL), median (range)	3422 (2110–6677)	5205 (2929–7407)	0.067*
NLR, median (range)	2.99 (1.07–7.86)	5.95 (1.86–7.17)	0.20*
CRP (mg/dL), median (range)	0.71 (0.09–10.84)	0.83 (0.25–3.1)	0.48*

ECOG PS Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *TMT* targeted molecular therapy, *RCC* renal cell carcinoma, *LDH* lactate dehydrogenase, *NLR* neutrophil-to-lymphocyte ratio, *CRP* C-reactive protein

* The *p* value was calculated using the Mann–Whitney *U* test

The *p* value was calculated using the chi-square test

IVC thrombus level in patients with RCC is limited to only selected patients.

We evaluated the change in the primary tumor with TMT and found that the median change in the primary tumor size was −4.5% (range −19.0 to 21.7). Moreover, we investigated the association between the effect of TMT on the IVC tumor thrombus and that on the primary tumor. Although the two variables tended to correlate, the correlation was not statistically significant. To our knowledge, no previous study has investigated this association. This result might be attributed to the heterogeneity of RCC.

As mentioned, only selected patients experienced a decrease in thrombus height and level. However, it is unclear which factors are associated with the effect of TMT on an IVC thrombus in patients with RCC. In our study, RCC patients with an IVC tumor thrombus having a clinical nodal stage of N2 or higher neutrophil count showed a poor benefit from TMT. To our knowledge, no studies have assessed the predictive factors for the effect of TMT on an IVC tumor thrombus in patients with RCC. However, nodal metastasis has been reported to correlate with survival in patients with an IVC tumor thrombus associated with RCC [21, 22]. Additionally, in the case of RCC, the absolute neutrophil count has been identified as an independent prognostic factor [23, 24]. Moreover, de Martino et al. reported that patients with an increase in the absolute neutrophil count showed an association with lymph node metastasis [25].

We attempted to determine which TMT was more effective for the IVC tumor thrombus and found that pazopanib therapy might be more effective; however, the sample size was very small. Thus, the most effective TMT remains to be determined.

Consistent with the findings of previous studies [13, 20], the present study found that TMT did not effectively decrease the IVC tumor thrombus in all patients with RCC, and about 20% of the patients treated with TMT experienced an increase in the IVC tumor thrombus during therapy. Considering these results, it appears better for patients with an IVC tumor thrombus associated with RCC to undergo surgery without pre-surgical TMT, if possible. Nonetheless, if the indication for pre-surgical TMT is considered, TMT might benefit patients without lymph node metastasis and a high neutrophil count who have a long waiting period before they undergo surgery.

The present study has several limitations. The study had a retrospective design and included a small number of patients. Moreover, the study included patients who received previous treatment, including surgery, before TMT therapy. We could not exclude patients who received previous treatment because of the small number of patients. Further prospective studies with larger numbers of patients are needed to overcome these limitations.

In conclusion, we demonstrated that the effect of TMT on an IVC thrombus associated with RCC is limited, and that the therapy might not be effective in patients with lymph node swelling.

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Compliance with ethical standards

Conflict of interest Tsunenori Kondo received honoraria from Bayer Yakuhin Ltd., Pfizer, and Novartis. All other authors declare no conflicts of interest with regard to this study.

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